Job No.: 1505-95836 Ref.: DE 4336299
Translated from German by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

FEDERAL REPUBLIC OF GERMANY
GERMAN PATENT OFFICE
PATENT NO. DE 43 36 299 A 1
(Offenlegungsschrift)

Int. Cl.[6]:	C 08 F 20/00 C 08 F 2/50 C 08 F 2/44 C 08 F 265/02 C 08 L 33/02 C 08 K 5/05 C 08 K 5/17 C 08 K 5/06 A 61 K 9/107 //C08F 20/06 C 08 J 5/04//
Filing No.:	P 43 36 299.0
Filing Date:	October 25, 1993
Publication Date:	May 11, 1995

GEL BODY FOR PERCUTANEOUS ADMINISTRATION, IN PARTICULAR OF MEDICATIONS

Inventor:	Johannes Anz 38820 Halberstadt, DE
Applicant:	Arbo-Robotron Medizin-Technologie GmbH 38820 Halberstadt, DE
Agent:	B. Tragsdorf Patent Attorney 06846 Dessau

Publications considered in determining patentability:

DE 39 03 672 C2
DE 37 44 289 A1
DE 37 30 289 A1
US 48 20 799
EP 04 55 458 A2
EP 04 36 203 A3
EP 04 35 200 A2

EP 04 35 199 A3
EP 03 05 175 A1
EP 03 03 445 A1
EP 00 86 997 A2
EP 00 20 905 A1
EP 5 31 938 A1
EP 4 39 344 A2
EP 4 38 215 A1
EP 4 36 203 A2
EP 4 35 200 A2
EP 4 35 199 A2
EP 3 03 445 A1
EP 2 63 605 A2
Georg Reinhard;
Eckhard Mersiowsky: Layer Formation-Electropolymerization of Acrylic Acid and Corrosion Protection - In: Farbe + Lack, Vol. 96, 12/1990, pp. 942-946;
Derwent Abstracts: Ref, 89-044024/06 to JP 3317-519-A;
Ref. 89-217496/30 to JP 1156-310-A;
Ref. 86-242883/37 to JP 1172-817-A;
Ref. 86-098113/15 to JP 1043-678-A;
Ref. 92-263000/32 to JP 04178323-A;

The following data are taken from documents submitted by the applicant.

[Abstract]

The invention concerns a gel body based on acrylic acid for administration, in particular of medications, through the skin of a mammal, especially humans.

Known gel bodies of this kind only have low material thickness, thus only low absorption capacity is available, and are limited in use to a few active agents. In addition, their manufacture is very expensive and cost-intensive and polymerization can take place only under an inert gas.

In order to remedy these disadvantages, a gel body is proposed that consists of a reaction mixture of ethylenically unsaturated acrylic acid-based monomers dissolved in an aqueous polyol-containing liquid, which is polymerized in situ under normal conditions with UV light. The gel body contains other additives such as initiators, coinitiators, cross-linking agents and polyacrylic acid.

Description

The invention concerns a gel based on acrylic acid for administration, especially of medications, through the skin of a mammal, especially humans.

Gel bodies of this kind are already known (EP 0 531 938, EP 0 436 203 and EP 0 435 199). They consist, for example, of 95 parts by weight 2-ethylhexyl acrylate and 5 parts acrylic acid, which are copolymerized under an inert gas in ethyl acetate as a solvent.

The solvent must be removed in a subsequent process step in order to produce on a solid substrate a pressure-sensitive adhesive film with very low thickness (under 300 μm), which is converted to its final form for use in subsequent process steps. Due to the low material thickness and low absorption capacity of the gel body its use is limited to only a few active agents. In addition, the diffusion behavior of the active agents into the skin and thus the deposition are very difficult to control.

The preparation of these gels is very expensive and gives rise to high costs. The polymerization reaction can take place only under an inert gas.

The invention was based on the task of developing a gel body for percutaneous administration, in particular of medications, which has high absorption capacity, can be bonded to the skin without additional auxiliary agents and has good adhesive effect during application. In addition, the gel body should be able to be produced simply and cheaply on an industrial scale.

In accordance with the invention the task is solved by the fact that the gel body consists of a reaction mixture of ethylenically unsaturated acrylic acid-based monomers dissolved in an aqueous polyol-containing liquid that is polymerized in situ with UV light under normal conditions.

Other embodiments are given below.

The aqueous polyol-containing liquid consists of demineralized water and polyols dissolved in it in a ratio of 1:0.5 to 1:5, and it can contain additional added agents.

The ethylenically unsaturated acrylic acid-based monomers are acrylic acid and its derivatives with a relative molecular weight up to 320. The acrylic acid-based monomers are stabilized with hydroquinone methyl ether. The additional added agents are initiators, coinitiators, cross-linking agents and polyacrylic acid.

Preferably, the reaction mixture consists of

a) 100 parts by weight ethylencially unsaturated stabilized acrylic acid-based monomers with a relative molecular weight of 72 to 320,

b) 275 to 600 parts by weight of an aqueous polyol-containing liquid of demineralized water and a polyol dissolved in it in a ratio of 1:1.5 to 1:3,

c) 0.1 to 8 parts by weight UV initiator,

d) 12 to 125 parts by weight of a secondary or a tertiary amine as coinitiator,

e) 2.5 to 12.5 parts by weight of a polyunsaturated compounds as cross-linking agent, and

f) 0.2 to 10 parts by weight polyacrylic acid with a relative molecular weight of 150,000 to 350,000.

Glycerol is particularly suited as the polyol. The amount of the UV initiator is preferably 0.5 to 5 parts by weight. Triethanolamine is used as the amine. The amount of the cross-linking agent is preferably 4.5 to 6.5 parts by weight.

Triethylene glycol dimethacrylate is preferably used as the cross-linking agent. The polyacrylic acid is added in particular in an amount from 2 to 5 parts by weight. The gel body can contain as additional added agents viscosity regulators, fragrances, inhibitors, electrolytes, bacteriostatic agents, indicators, colorants, complexing agents, buffers or compatibility aids in a total amount up to 35 parts by weight.

In addition, the gel body can be provided with textile inserts.

The gel body in accordance with the invention can be produced simply and cheaply and has excellent properties for deposition and uniform re-release of active agents in medical use. Such active agents can be ones that act directly on the skin, for example test substances for evaluating skin reactions (epicutaneous tests), or topical remedies, as well as ones that pass into the body via the skin and the circulatory system.

Among these are active agents that were already applied topically in order to be effective in surrounding body regions, for example rubs, salves, antirheumatic plasters or poultices, on ones whose efficacy would be reduced or destroyed if administered via the digestive tract.

Compared to administration via carriers that adhere to the mucosa, which are also already known, the gel body in accordance with the invention has the advantage that other restrictions connected with mucoadhesive application can be circumvented, for example irritation of the sensitive mucous membrane, reactions with saliva, losses of active agent through passage into the digestive tract, inadvertent swallowing, hindrance when eating and speaking, toxic reactions of active agents upon absorption in the digestive tract, poor characteristic taste or odor of the active agent.

The gel body has the advantageous property of rapidly absorbing both dry active agents as well as the conventional aqueous or alcoholic dilutions of active agents in order to release them to the skin over a lengthy period of time through concentration-equalizing diffusion processes upon subsequent application. Subsequently applied active agents remain bonded on the gel body surface because of its characteristic adhesiveness. The active agents can be incorporated into the gel body during its manufacture, but especially before application, in each case according to use, through external application, such as adding by drops or by adhesion, or by injection into the interior of the gel body. In special cases it is also conceivable to introduce or

supplement amounts of active agent after application of the gel body to the skin via the side turned away from the skin. The gel body in an appropriate skin application is barely perceived by the wearer (patient) as annoying at all.

The gel body itself is chemically inert with respect to most active agents and maintains its consistency because of its polymer network matrix. Its adhesiveness to the skin can be adjusted, so that it is possible to do entirely without additional bonding aids and also to match it to any skin type. Its high long-term elasticity is not affected either by storage or by application, so that a sound skin contact is ensured. After effortless peeling from the skin, there remain practically no troublesome residues.

The transparency of the gel body allows continuous observation of the covered skin surface, which favors its use in the field of induced skin reactions, in which the contact allergen is supposed to act on the skin without interruption for an established contact time of, 24 hours, under seal (occlusion). Its own skin neutrality, which has been seen with few exceptions, excludes false skin reactions caused by the gel body itself.

Shortly after application of the gel body to the skin, moisture equilibrium with the skin is established, which initiates the release of the active agent.

The actual gel body with its adhesive surface is substantially homogeneous, and embedding textile inserts in it, for example, or applying it to solid substrates, which is favorable for some applications, are also possible.

It is made, especially when incorporated into manufacture of strips, by substance polymerization of an aqueous polyol-containing liquid reaction mixture based on ethylenically unsaturated monomers initiated by UV irradiation without exclusion of atmospheric oxygen. Various embodiments are conceivable, in each case according to use. Thus, the thickness of the layer can be varied between 0.3 and 10 mm by controlling the diffusion rate. Besides the production of flat products, plaster-like individual products of any shape and size with and without additional adhesive surfaces surrounding the gel body can be produced. Moreover, special embodiments are conceivable, for example the introduction of recesses to hold the active agent, on combining it with other materials, for example to achieve additional mechanical marking of the skin in an allergy test.

The gel body is usually covered on the side turned away from the skin by a sheet material, which serves as a substrate for holding the reaction mixture during the polymerization of the gel body. Such sheets can be made as desired from material, as is most favorable for production and use. There is a wide range of available woven and nonwoven textiles and closed-cell foamed or compact plastic sheets with or without hypoallergenic adhesive coatings, which can be joined to the gel body individually or in combination during its manufacture. They must

not separate from the gel body unintentionally before and during application, must be sufficiently flexible and, as a rule, should be transparent or at least translucent.

The site of the gel body turned to the skin is covered with an antiadhesive paper or film strip before use.

The invention is to be illustrated below by means of some examples.

Example 1

A typical application of the gel body in accordance with the invention is used in a test plaster for testing contact allergens.

In an electronically controlled device operating in uniform steps with a transport unit a plaster body is prepared, which has a recess provided for the gel body and the following composition: the plaster body is composed of a skin-compatible adhesive-coated flexible carrier layer – for example a PE film with thickness 150 μm, such as is sold by the Medifix Co. (GB) – with a ring 2 mm high and 18 or 22 mm diameter of PE foam (Vito Irmen Co.) set on the adhesive side. The recess formed by the carrier layer and the foam ring is filled by means of a dispensing device with the reaction solution, which has been adjusted rheologically to the advance motion of the transport device; the solution has the following composition and was prepared beforehand under exclusion of light in a stainless steel vessel with about twice the ultimate volume with intimate mixing (amounts in parts by weight):

100	Acrylic acid stabilized with 0.05 parts by weight hydroquinone methyl ether (pure)
3.5	Photoinitiator, Irgacure 184 (Ciba Geigy)
280	Glycerol (86%)
130	Demineralized water
50	Coinitiator: triethanolamine (pure)
5.3	Cross linker, triethylene glycol dimethacrylate (pure)
3.0	Polyacrylic acid (Goodrite K702, 25% in water, M_r = 240,000)
10	Viscosity regulator: amylopectin (cooked)

The reaction mixture is polymerized for a period of about 80 seconds in the subsequent UV section, which is equipped with Hönle UV 400 H emitters. After leaving the UV section the tacky topside of the strip is covered with a siliconized plastic strip (for example Perlasic LF; Papierfabrik Perlen, Switzerland) and the complete plaster is stamped out (50 mm diameter) so that the gel body sits in the middle. Then quality testing was carried out:

The plasters were used to test the following contact allergens for appropriately chosen known sensitized persons and applied after about 20 minutes absorption for the liquids for a maximum of 24 hours:

- Nickel sulfate, 5% in water, about 0.01 mL dropped in the middle
- Peru balsam, 25% in ethanol, about 0.01 mL dropped in the middle
- Fresh plant parts (Arnica), ground, about 2 x 6 mm^2 exposure
- Rabbit hair, about 10 pieces
- For comparison without test substance

Even though the skin reactions frequently did not develop for a period up to 3 days after removal of the test plaster, in the case of contact with nickel sulfate and rabbit hair visible skin reactions could be observed by the test subjects themselves only a few hours after contact, which would not be possible in the case of a nontransparent cover. After removal of the test plasters the gel body was still tacky. Small residues on the skin in the outer edge region of the carrier material were easily removed with ethanol.

A slight skin reaction (reddening) in the region of the gel was observed only in one case, in which the corresponding irritation occurred in the remaining area of the cover because of the adhesive edge.

Example 2

As in Example 1, a transparent polymer strip of PE with one-sided hypoallergenic adhesive coating is sent to the stepped conveyor device. However, this time the recess for holding the gel body is formed by thermoforming with a depth of 2.5 mm.

A reaction solution is dispensed into this cavity; it has the following composition and was processed as in Example 1 (date in parts by weight):

100	Acrylic acid stabilized with 0.05 parts by weight hydroquinone methyl ether (pure)
300	Glycerol (86%)
150	Demineralized water
3.5	Photoinitiator, Karocur 1173 (Ciba Geigy)
58.8	Coinitiator: triethanol amine (pure)
5.3	Cross-linking agent: triethylene glycol dimethacrylate (pure)
3.0	Polyacrylic acid (Goodrite K702, 25% in water)
9.5	Viscosity regulator, amylopectin (cooked)

As in Example 1, the reaction mixture was polymerized for a time of about 70 seconds, then the top side of the strip was covered and then the plasters were cut out (diameter 45 mm).

The plasters were tested by analogy with Example 1 and the same results were achieved.

Example 3

As in Examples 1 and 2, a flexible transparent polymer strip of polyethylene is sent to the said device. First the siliconized cover paper situated between the //section// is evenly peeled off from above. A textile nonwoven strip based on viscose fibers (Norafin, 35 g/m^2, composite and nonwovens, Wiesenbad GmbH) is rolled out and pressed onto the adhesive-coated surface of the PE film. The reaction mixture forming the hydrogel is applied to this nonwoven and distributed on it. The reaction mixture is rheologically adjusted so that the necessary layer thickness of the gel body, of about 1.6 mm, is achieved. The composition corresponds to that of Example 2.

The reaction mixture is exposed to UV light in the UV section for a period of about 105 seconds and polymerized. After leaving the UV section the tacky gel top upper side is covered with a siliconized plastic strip (for example Perlasic LF; Papierfabrik Perlen, Switzerland). Transparent plasters (30 mm diameter) are cut down to the siliconized plastic strip by means of a knife cutter at distances of 35 mm and the remainder is peeled off. The siliconized strip with the plasters adhering to it is packaged as required.

The plasters were tested as in Example 1, where the results show the following changes in a comparison with Example 1.

The very much milder adhesion of the gel to the skin compared to the conventional adhesive coating that was used for additional securing resulted in the nonspecific skin reactions that are conventional after peeling off in the adhesion region not to appear. The self-adhesive gel practically puts no stress on the skin when being peeled off. The actual test goal was not masked.

Example 4

By analogy with Example 3, a plaster without an outer adhesive edge was prepared, but with the difference that instead of PE film as carrier material an adhesive-coated nonwoven material was used, as is sold under the designation 5021 by the Norgesplaster Co. (Norway) and with the difference that this plaster has a rectangular shape with rounded corners measuring 60 mm x 180 mm.

This plaster was provided with active agent in the amount of 100 mg ibuprofen (15% solution) on the gel side 5 minutes before application and bonded to the affected sites for wearing time of at least 24 hours in the usual way, for example for treating inflammatory rheumatic diseases of the spinal column. The amount of active agent was refreshed at period from 6 to 12 hours through the outer nonwoven layer.

Example 5

By analogy with Example 4 a round plaster 35 mm in diameter is supplied with Silica D4 (alcoholic solution) for homeopathic treatment of a cyst on the instep of a patient. With an initial

dosage of 0.08 mL solution administered via the outer nonwoven strip the plaster was glued to the corresponding site; 2 times daily a supplemental dosage of 0.03 mL was added. One plaster can be worn about 6 days. After an interruption of about 2 hours the next plaster can be administered in the same way.

The topical use is usually supported by oral administration dosages.

Claims

1. A gel body for percutaneous administration, especially of medications, based on acrylic acid, which is characterized by the fact that it consists of a reaction mixture of an ethylenically unsaturated monomer based on acrylic acid dissolved in an aqueous polyol-containing liquid, which is polymerized in situ under normal conditions with UV light.

2. A gel body as in Claim 1, which is characterized by the fact that the aqueous polyol-containing liquid consists of demineralized water and polyols dissolved therein in a 1:0.5 to 1:5 ratio and other additives are contained in it.

3. A gel body as in Claim 1 or 2, which is characterized by the fact that the ethylenically unsaturated monomer based on acrylic acid are acrylic acid and their derivatives with a relative molecular weight up to 320.

4. A gel body as in one of Claims 1 to 3, which is characterized by the fact that the monomers based on acrylic acid are stabilized with hydroquinone methyl ether.

5. A gel body as in one of Claims 1 to 4, which is characterized by the fact that the other additives are initiators, coinitiators, cross linkers and polyacrylic acid.

6. A gel body as in one of Claims 1 to 5, which is characterized by the fact that the reaction mixture consists of

a) 100 parts by weight ethylenically unsaturated stabilized acrylic acid-based monomers with a relative molecular weight of 72 to 320,

b) 275 to 600 parts by weight of an aqueous polyol-containing liquid of demineralized water and a polyol dissolved in it in a ratio of 1:1.5 to 1:3,

c) 0.1 to 8 parts by weight UV initiator,

d) 12 to 125 parts by weight of a secondary or a tertiary amine as coinitiator,

e) 2.5 to 12.5 parts by weight of a polyunsaturated compounds as cross-linking agent, and

f) 0.2 to 10 parts by weight polyacrylic acid with a relative molecular weight of 150,000 to 350,000.

7. A gel body as in one of Claims 1 to 6, which is characterized by the fact that the polyol is glycerol.

8. A gel body as in one of Claims 1 to 7, which is characterized by the fact that the fact that the amount of the UV initiator is 0.5 to 5 parts by weight.

9. A gel body as in one of Claims 1 to 8, which is characterized by the fact that the amount of the amine is 45 to 75 parts by weight.

10. A gel body as in one of Claims 1 to 9, which is characterized by the fact that the amine is triethanolamine.

11. A gel body as in one of Claims 1 to 10, which is characterized by the fact that the amount of the cross linker is 4.5 to 6.5 parts by weight.

12. A gel body as in one of Claims 1 to 11, which is characterized by the fact that the cross-linking agent is triethylene glycol dimethacrylate.

13. A gel body as in one of Claims 1 to 12, which is characterized by the fact that the amount of polyacrylic acid is 2 to 5 parts by weight.

14. A gel body as in one of Claims 1 to 13, which is characterized by the fact that it contains as additional additives viscosity regulators, fragrances, inhibitors, electrolytes, bacteriostatic agents, indicators, colorants, complexing agents, buffers or compatibility aids in a total amount up to 35 parts by weight.

15. A gel body as in one of Claims 1 to 14, which is characterized by the fact that it contains textile inserts.

16. A gel body as in one of Claims 1 to 15, which is characterized by the fact that it contains recesses to hold active agents.

17. A gel body as in one of Claims 1 to 16, which is characterized by the fact that it is provided on the side turned toward the skin with elevations or the like that give rise to visible markings during the application on the skin.